

# Human Bioaccumulation Potential Simulated in R and Implemented in KNIME



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## Introduction and Aims

The assessment of human bioaccumulation potential is an important element in the risk assessment of chemicals. Tonnelier et al. (Arch Toxicol (2012) 86: 393–403) developed a generic physiologically based toxicokinetic (PBTk) model which, based on *in vitro* human liver metabolism data, minimal renal excretion and a constant exposure, was able to predict the bioaccumulation potential of chemicals. This model was designed to incorporate not only the chemical properties of the compounds, but also the processes that tend to decrease the concentration of the compound, such as metabolism. Following this work we have implemented the generic PBTk model, now written in R, in the open source KNIME interface.

## Methods

The KNIME workflow consists of several nodes (Figure 1):

1. A database connection consisting of a connector;
2. A query filter node to select the values for the simulated chemical. In this specific node the MySQL database (version 5.5) is connected with the driver;
3. In parallel an XLS reader node reports the model parameters (e.g. flow rates, volume of organs, etc.) for input data into the model;
4. An R node where the PBTk model is described;
5. An R view node for output.

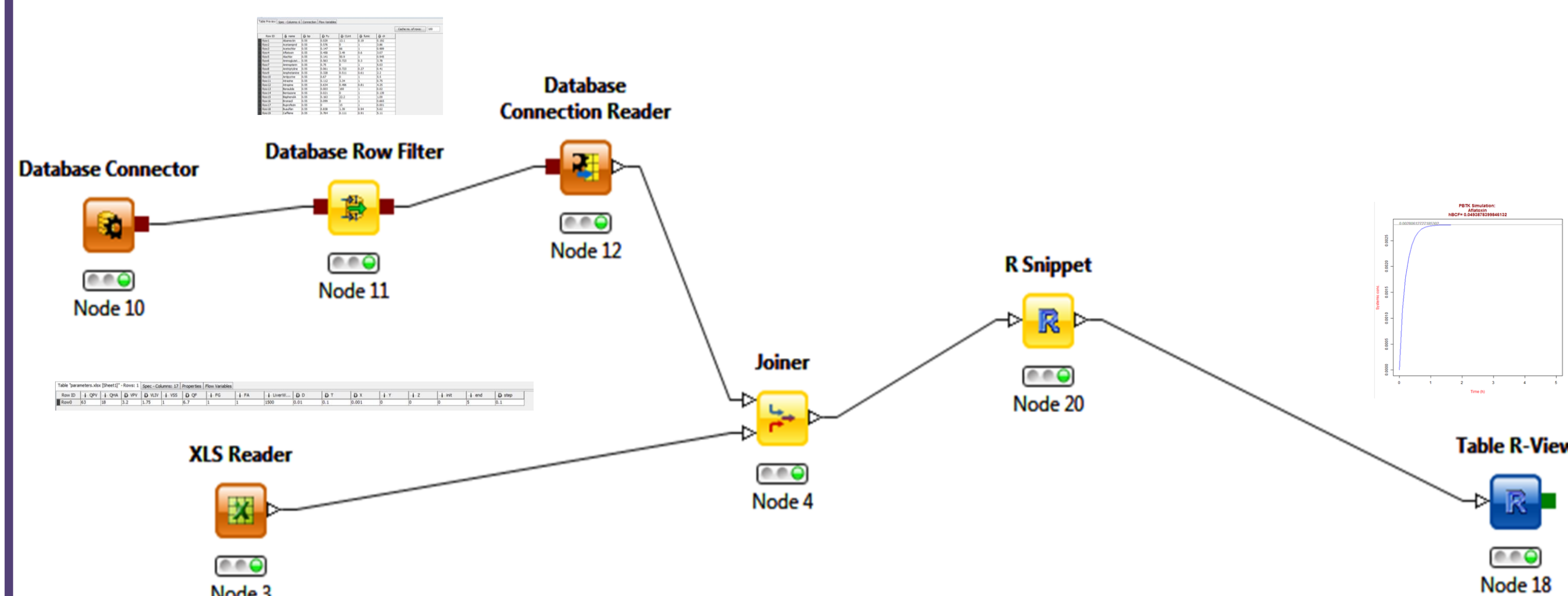


Figure 1. KNIME interface for human bioaccumulation

Based on Tonnelier et al. (2012) the simplified PBTk model was re-written in R. The three compartments (plus uptake) physiologically based model are reported here:

$$V_{PV} \frac{dC_{PV}}{dt} = Q_{PV} (C_{sys} - C_{PV}) + k_a A(t)$$

$$V_{liv} \frac{dC_{liv}}{dt} = Q_{PV} (C_{PV} - C_{liv}) + Q_{HA} (C_{sys} - C_{liv}) - CL_H C_{liv}$$

$$V_{SS} \frac{dC_{sys}}{dt} = Q_{PV} (C_{liv} - C_{sys}) + Q_{HA} (C_{liv} - C_{sys}) - CL_R C_{sys}$$

$$\frac{dA}{dt} = -ka A(t)$$

$$\text{Human bioconcentration factor hBCF} \rightarrow hBCF = \frac{C_{sys}^*}{D/T} V_{PV} / t$$

## Reference

Tonnelier A, Coecke S, Zaldívar JM (2012) Screening of chemicals for human bioaccumulative potential with a physiologically based toxicokinetic model. Arch. Toxicol. 86: 393-403.

## Results

The PBTk model implemented in the KNIME interface was used to simulate the systemic concentration at steady state ( $C_{sys}$ ) of chemicals (Figure 2) from which the hBCF was calculated (Table 1).

Figure 3 reports our results compared to the one from Tonnelier et al. (2012), the results are within the same order of magnitude (with exception of PFOS). However, as reported in Table 2 the potency ranking is slightly different between the two studies.

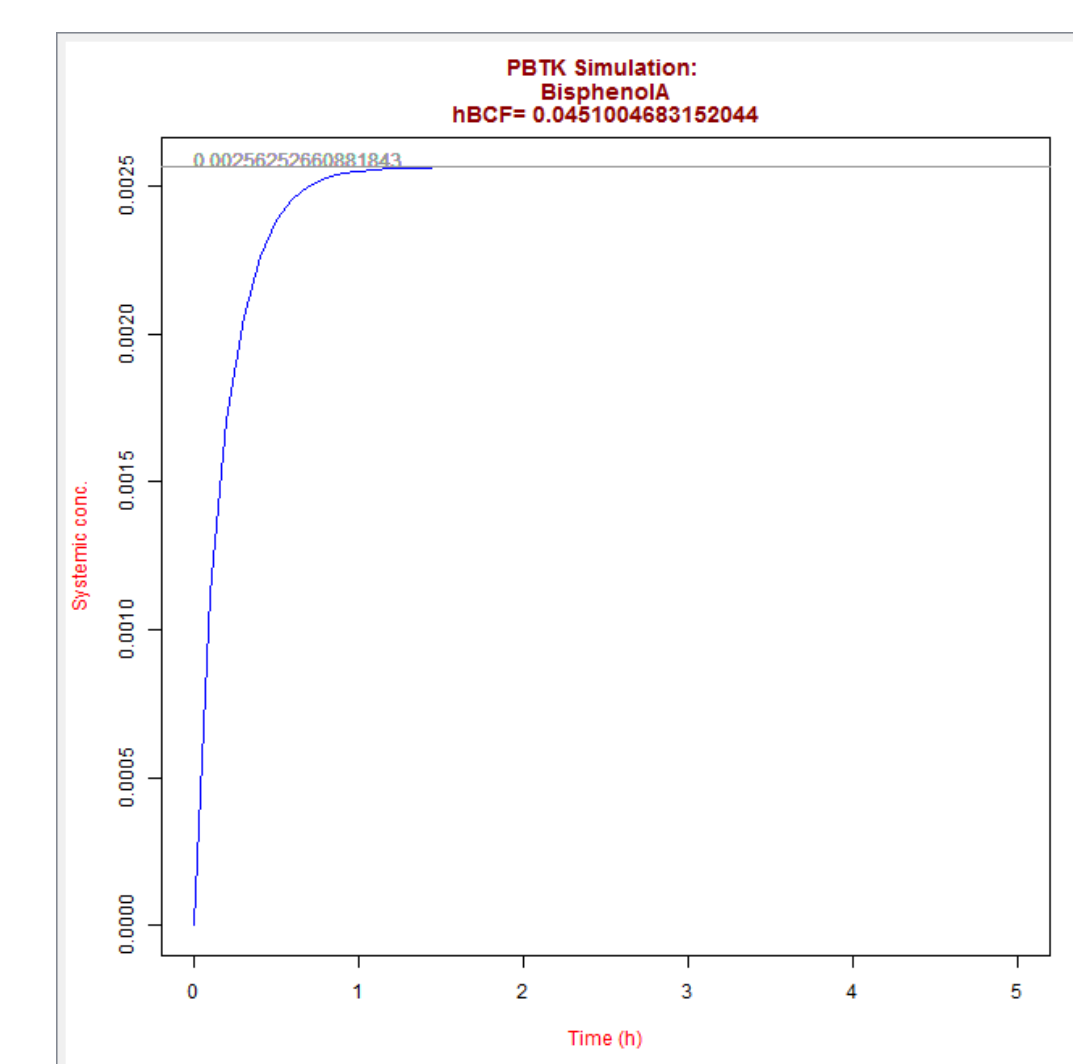


Figure 2. Simulation of the PBTk model at 0.01mg dose of compound.

Table 1.  $C_{sys}$  values and hBCF values calculated with the KNIME interface.

Name	$C_{sys}$ (μM)	hBCF (L*kg <sup>-1</sup> )	Name	$C_{sys}$ (μM)	hBCF (L*kg <sup>-1</sup> )
Emamectin	21.3	375.3	Parathion	0.29	5
PCB155	2.98	52.54	Cyprodinil	0.26	4.68
PCB153	2.98	52.53	DDT	0.25	4.3
PCB80	2.98	52.53	Pyraclostrobin	0.19	3.3
PCB77	2.98	52.53	Bromacil	0.15	2.65
PCB136	2.98	52.49	Fipronil	0.13	2.24
Bupropion	1.70	29.84	Warfarin	0.11	1.96
Fenvalerate	0.94	16.43	Thiodiazine	0.11	1.95
Bentazone	0.71	12.69	Fenoxycarb	0.09	1.56
Dichlorophenoxy	0.34	5.957	Ibuprofen	0.09	1.55

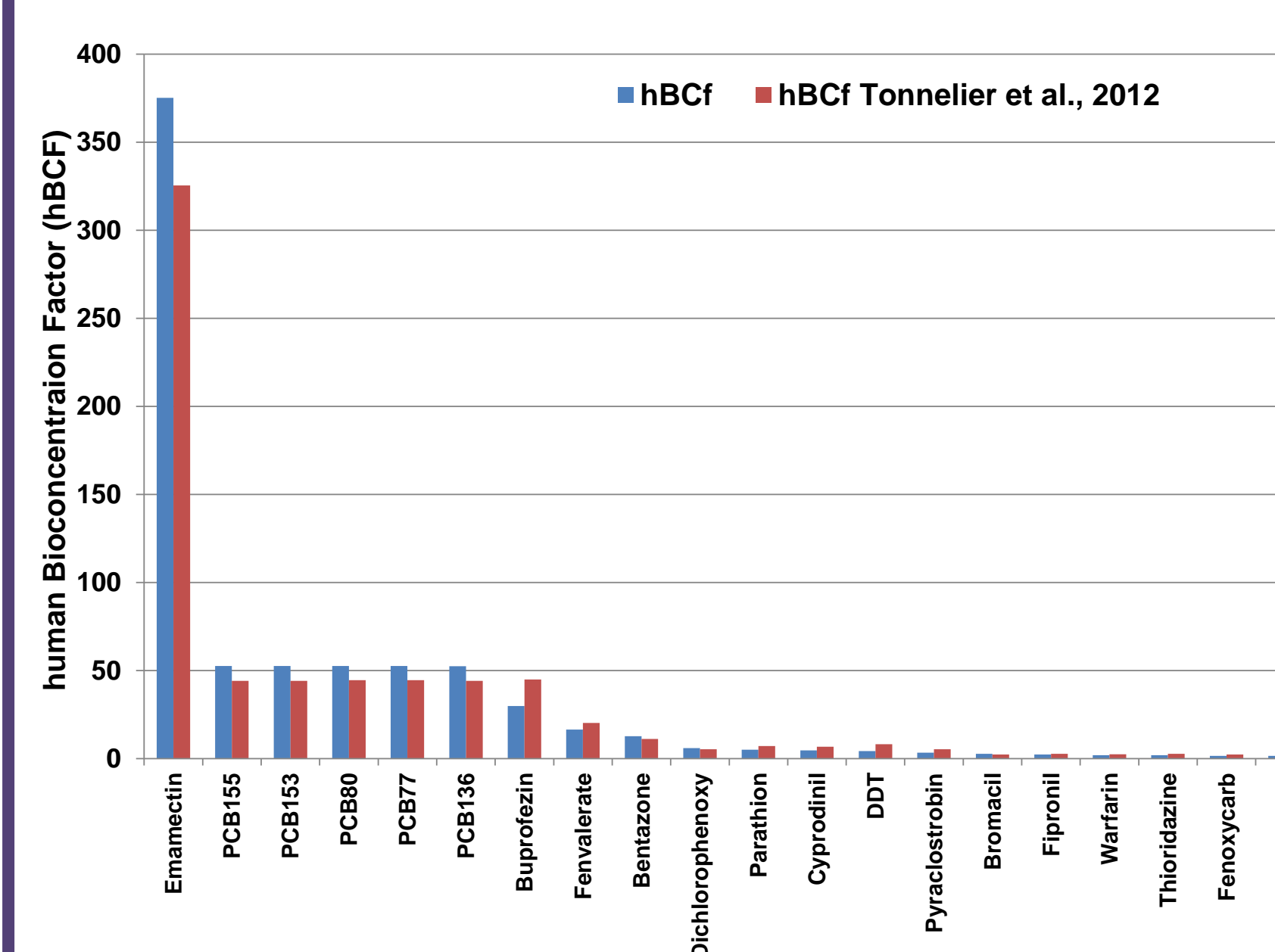


Figure 3. hBCF calculated with the KNIME interface versus values obtained by Tonnelier et al., 2012.

Table 2. Potency ranking from this study versus Tonnelier et al., 2012.

Chemical KNIME	Chemical Tonnelier et al., 2012
Emamectin	PFOS
PCB155	Emamectin
PCB153	Bupropion
PCB80	PCB80
PCB77	PCB77
PCB136	PCB153
Bupropion	PCB155
Fenvalerate	PCB136
PFOS	Fenvalerate
Bentazone	Bentazone
Dichlorophenoxy	DDT
Parathion	Parathion
Cyprodinil	Cyprodinil
DDT	Pyraclostrobin
Pyraclostrobin	Dichlorophenoxy
Bromacil	Fipronil
Fipronil	Thiodiazine
Warfarin	Warfarin
Thiodiazine	Bromacil
Fenoxycarb	Fenoxycarb

## Conclusions

- The human bioconcentration factor (hBCF) can be estimated using this new developed tool built using the KNIME interface!
- The hBCF calculated with KNIME interface were in the same order of magnitude as reported previously, but the potency ranking was slightly different; this will be investigated further!
- A direct and straightforward estimation of the hBCF based solely on a limited number of compound parameters would be of advantage in prioritisation of chemicals and may provide an efficient pre-screening criterion for a rapid assessment. This approach can be applied in the assessment of cosmetics ingredients!

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